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Final Report
for:

ONR Contract N00014-88-K-0513

To:

Dr. James M. Bower

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California Institute of Technology
Pasadena, CA.

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Summary

Over the last three years we made significant progress in the work supported by this contract. Progress has been made in theoretical modeling, in physiological experiments, and in behaviorally testing. Progress in each of these areas is summarized in the following sections:

1. *Modeling the dynamical properties of olfactory cortex.* In parallel with experimental studies on the olfactory system, we have developed detailed, biologically realistic simulations within which to study the computational properties of the olfactory system. Much of this work has concentrated on our efforts to model the olfactory, or piriform, cortex. The initial phases of this modeling effort consisted of an attempt to reconstruct the complex spatial and temporal patterns of cortical activity induced by natural and artificial stimuli using a structurally realistic model (Wilson and Bower, 1989; 1990; Bower, 1990a, 1990b). The results, as described in numerous publications, have revealed new mechanisms for the generation of oscillatory responses within this cortex. These modeling results have also suggested new ideas regarding the functional significance of the oscillatory patterns for olfactory processing in this network (Bower, 1990a). With reports that other cerebral cortical areas also have oscillatory properties (Ekhorn et al., 1988; Gray et al., 1989), we sought to extend our piriform cortex results to neo-cortical areas. The results have important implications for the interpretation of oscillatory behavior in these other cortical regions (see Wilson and Bower, 1990b; 1991).

2. *Modeling the possible associative memory function of olfactory cortex.* A second major focus of our modeling effort has been on the possible associative memory properties of the piriform cortex. This work was based on our view that there is a close linkage between associative memory function and the basic task of odor recognition within the olfactory system (Bower, 1991a; 1991b). To study the auto-association memory capacity of the piriform cortex network, the model just described was provided with input intended to loosely represent the activity of single neurons in the olfactory bulb (Wilson and Bower, 1988). Synaptic connections between bulbar neurons and neurons in the olfactory cortex were assigned completely randomly, as were the initial weights of each connection. In order to explore learning in the network, a Hebb-type correlation learning rule was also introduced to govern activity dependent changes in the synaptic strengths of modeled connections. At the time when these simulations were performed, no information was yet available on the existence or form of synaptic modification in piriform cortex, but evidence for Hebb-type synaptic modification did exist in the closely related hippocampus, and Hebbian learning rules provide the auto-correlation capacity of many abstract

auto-associative models (Hasselmo et al., 1991).

While the learning of natural olfactory stimuli undoubtedly requires quite complex network properties, in our investigations of our cortical model we concentrated on two relatively simple aspects of associative learning. First, we studied the capacity of the model to converge on consistent patterns of neuronal activity in response to particular input patterns. Presumably if the olfactory cortex is responsible for odor recognition, it should be able to generate consistent neuronal output in the presence of consistent neuronal input. Second, we studied the capacity of the model to generate a stable pattern of neuronal activity in the presence of an incomplete version of the input stimulus. Because the mix of molecules being emitted by any object can vary with, for example, its age or environmental circumstances, it is presumed that olfactory recognition must, to some extent, be insensitive to these variations (see Bower, 1991b).

Our modeling effort has shown that under the right network conditions, the model is capable of learning to generate a stable output when presented with a consistent input pattern. Specifically when synaptic modification was allowed under the same stimulus conditions, the network converged to a stable pattern of neuronal response after several stimulus presentations. We have also shown that the network is capable of learning to generate different patterns of activity in response to different patterns of input. With respect to the process of pattern completion, we have shown that, once learned, our model is able to generate a stable output even in the presence of changes in the input pattern. In particular, when the number of active bulbar inputs was reduced by half, the response of the network to the original full pattern of stimulation was maintained (Wilson and Bower, 1988).

While it was important to show that a model structured like the olfactory cortex is capable of performing such basic associative memory functions, the more important consequences of this modeling effort involve predications we were allowed to make concerning the network conditions that promoted these capacities. Specifically, we found that the associative memory capacity of the piriform cortex model was dependent on the specific presence of Hebb-type learning in the intrinsic fiber synapses (Wilson and Bower, 1988; Hasselmo et al, 1991a; 1991b) *and not the afferent synapses.* When synaptic modification was limited to synapses associated with the afferent fiber system, the network did not converge to a stable output pattern in response to a consistent input. The capacity for completion of incomplete input patterns also depended on which set of synapses showed modification. When only afferent fibers were modifiable during learning, the system showed considerably less completion than when intrinsic fiber synapses were modifiable. Doubling the gain of afferent fiber modification actually reduced the level of completion, while doubling the gain of the intrinsic fiber learning rule provided almost 100% completion of the input pattern. Accordingly, the clear prediction from these results was that synapses of the intrinsic association fiber system should represent the principal site of synaptic learning in the olfactory cortex. As discussed in the physiology section below, this prediction has subsequently been confirmed using experimental procedures.

3. *Physiological investigations of synaptic plasticity in olfactory cortex.* As just described the model of associative learning in olfactory cortex made two predictions that were experimentally testable. First, the model suggested that synapses associated with the afferent projection fibers should be relatively unmodifiable. Second the model predicted that synapses associated with the intrinsic association fiber system should be capable of much more substantial modification. In the case of the afferent projections, the balance of the data already indicates that these synapses show neither short-term nor substantial long-term potentiation. However, it has only been recently that careful comparisons between afferent and intrinsic synaptic properties have been made. Motivated by our modeling results, we have conducted a series of experiments which demonstrate that synaptic potentials evoked by intrinsic fiber stimulation show clear and consistent short-term potentiation at frequencies which elicit no change or depression of synaptic potentials evoked by afferent fiber stimulation (Hasselmo and Bower, 1990a). Further, an *in vitro* experiment using extracellular recording techniques, performed subsequent to the simulations described above but naive with respect to the modeling results, shows a significantly greater level of long-term potentiation in intrinsic than afferent fiber synaptic potentials. These

perimental results are clea in good agreement with the model's prediction that synaptic odification should appear p marily in the intrinsic fiber synapses.

4. *Role of neuromodula s in cortical function.* Having demonstrated using modeling techques that different functio consequences can result from differences in the physiological operties of the two excitato fiber systems in this cortex, and, further, having determined experimentally that these diffe ces exist, we were interested in experimentally determining if ere were any additional dif rences in these synaptic populations. For these studies we elected explore the possible influc es of neuromodulatory agents with known behavioral effects on emory acquisition or retenti n. In our recent experiments of this type, we have focused on the le of cholinergic innervatio of piriform cortex (Hasselmo and Bower, 1991a; 1991b). Both e piriform cortex and olfac ry bulb appear to receive extensive cholinergic innervation from a gion of the basal forebrain, he horizontal limb of the diagonal band of Broca. Cholinergic tagonists have been shown to impair learning of new information in humans. In addition, the emory and cognitive impairments associated with Alzheimer's disease have been proposed to relatedto a loss of cholinergic innervation of cortical regions. These impairments include a creased capacity to identify olfactory stimuli.

The results of these experiments demonstrated marked differences in the suppression of transmission between the two excitatory synaptic populations. The acetylcholine agonist carbachol strongly suppresses synaptic potentials elicited by intrinsic fiber stimulation, decreasing the height of potentials by over 50% at concentrations less than 5uM, and by over 90% at 100uM (Hasselmo and Bower, 1990b; 1991a; 1991b). In contrast, carbachol reduced the height of afferent fiber synaptic potentials by less than 12%, even at a concentration of 500uM. This differential effect on afferent and intrinsic fiber synaptic potentials appeared whether they were recorded extracellularly from the layer being stimulated or intracellularly from the same piriform cortex pyramidal cell. Thus cholinergic modulation of synaptic function is directed at precisely those cortical synapses that our previous modeling work suggested are critical for memory function in this network.

5. *Modeling the possible effects of cholinergic modulation in olfactory cortex.* Recently, we have extended our modeling efforts to explore the possible consequences of our modeling inspired experimental discovery of a selective effect of the neuromodulatory agent acetylcholine on the intrinsic excitatory connections of this cortex. Initially, using a simplified model of the olfactory cortex, we demonstrated that this effect of acetylcholine may very well serve to increase the capacity of the piriform cortex for storing distinct memories without contamination with other memories (Hasselmo et al., 1991). Further, we have recently shown that associative functions like pattern completion are enhanced when the association fiber system is strong (i.e. in the absence of acetylcholine). These results suggest that this neuromodulator may be switching the network back and forth from a learning to a recall state, which in turn has allowed us to propose a new hypothesis regarding the role of acetylcholine in the memory function of cerebral cortical networks. We are now in the process of extending these results to our more complex model of the olfactory cortex.

6. *Broader significance of these results.* Our demonstration that there may be a functional odulation of the ability of the piriform cortex to store memory patterns has important implications for other memory models, including more abstract neuronal network models. Because memory storage in an auto-associative network is highly distributed, each memory shares some overlapping set of units or neurons with other memories. As the number of memories stored in a particular network increases, the amount of overlap goes up, raising the possibility that a particular input pattern will generate an output composed of a combination of multiple emories. Thus, a chief limitation on the storage capacity of an association memory network of e type considered here is overlap of patterns stored in the network. In abstract models of sociative memory, the problem of overlap is usually dealt with by constructing input patterns ith as little overlap as possible, or by pre- processing the input with a separate network using

anti-Hebbian learning rules. However, these separation techniques have the potential to interfere with the associative memory function of such networks in which the association of different stored memories is important. Our current modeling work suggests that, in the absence of acetylcholine, the stronger association fiber synaptic connections within the network may subserve this kind of associative function. Our discovery of a selective cholinergic suppression of intrinsic excitatory synapses therefore raises the possibility that cholinergic agonists may switch the network between a memory storage mode and a memory recall mode, thus providing multiple memory functions in a single network.

B. Publications resulting from contract.

Accepted or in press:

Hasselmo, M.E. and Bower, J.M. Cholinergic suppression specific to intrinsic not afferent fiber synapses in rat piriform (olfactory) cortex. J. Neurophysiol. (Accepted 1/12/91).

Hasselmo, M.E., Anderson, B.P., and Bower, J.M. Cholinergic modulation of cortical associative memory function. J. Neurophysiol. (Accepted 1/12/91).

Wilson, M. and Bower, J.M. Simulating cerebral cortical networks: oscillations and temporal interactions in a computer simulation of piriform (olfactory) cortex. J. Neurophysiol. (in press).

Bower, J.M. Piriform cortex and olfactory object recognition. In: J. Davis and H. Eichenbaum (Eds.) Olfaction as a Model System for Computational Neuroscience, MIT Press, Cambridge, MA. (in press).

Bower, J.M. Associative memory in a biological network: Structural stimulations of the olfactory cerebral cortex. In: Miltunovic and Antognetti (Eds.) Neural Networks Vol. II. Prentice Hall, New Jersey. (in press).

1991

Hasselmo, M.E., Wilson, M.A., Anderson, B., and Bower, J.M. 1991 Associative function in piriform (olfactory) cortex: Computational modeling and neuropharmacology. In: The Brain, Cold Spring Harbor Symposium on Quantitative Biology, Volume LV. Cold Spring Harbor Press, Cold Spring Harbor, New York. pp. 599-610.

Hasselmo, M.E., Anderson, B.P., and Bower, J.M. 1991 Cholinergic modulation may enhance cortical associative memory function. Advances in Neural information processing systems, Vol. 3, R.P. Lippman, J. Moody, and D. S. Touretzky, editor. Morgan Kaufmann, San Mateo, CA, pp. 46-52.

Hasselmo, M.E. and Bower, J.M. 1991 Selective suppression of afferent not intrinsic fiber synaptic transmission by 2-amino-4-phosphonobutyric acid in rat piriform cortex. Brain Research 548: 248-255.

Wilson, M.A. and Bower, J.M. 1991 A computer simulation of oscillatory behavior in primary visual cerebral cortex. Neural computation 3.

1990

Bower, J.M. 1990 I erse engineering the nervous system: An anatomical, physiological, and computer ba approach. In: An Introduction to Neural and Electronic Networks. S. Zornetzer, J. Da and C. Lau, editors. Academic Press pp. 3-24.

Hasselmo, M.E. an Bower, J.M. 1990 Afferent and association fiber differences in short-term potentiatio piriform (olfactory) cortex. J. Neurophysiol. 64: 179-190.

Nelson. M.E. and J er, J.M. 1990 Brain maps and parallel computers. Trends in Neuroscience 1. 403-408.

Nelson, M.E. and J er, J.M. 1990 Computational efficiency: A common organizing principle for par l computer maps and brain maps. Advances in Neural information processing syst . Vol. 2, D. Touretzky, editor. Morgan Kaufmann, San Mateo, CA , pp. 60-67.

Wilson, M.A. and wer, J.M. 1990 Computer simulation of oscillatory behavior in cerebral cortica tworks. Advances in Neural information processing systems. Vol. 2, D. Touretzky, or. Morgan Kaufmann, San Mateo, CA., pp. 84-91.

1989

Haberly, L.B. and M. Bower. 1989 Olfactory cortex: Model circuit for study of associative me ry? Trends in Neurosci. 12: 258 - 264.

Nelson, M., Furm ki, W. and J.M. Bower. 1989 Simulating neurons and neuronal networks on parallel co ters. In: Methods in Neuronal Modeling: From Synapses to Networks. C. Koch and I. gev, editors. MIT Press, Cambridge, MA., pp 397-438.

Wilson, M. and J. Bower. 1989 The simulation of large-scale neuronal networks. In: Methods in N nal Modeling: From Synapses to Networks. C. Koch and I. Segev, editors. MIT Pre Cambridge, MA.. pp. 291-334.

1988

Bower, J.M., Nel n, M.E., Wilson, M.A., Fox, G.C. and W. Furmanski. 1988 Piriform (Olfactory) co x model on the hypercube. Proceedings of 3rd conference on hypercube concurrent co uters & applications. ACM, New York, NY. pp. 977-999.

Bower, J.M., Wi n, M. Banik, J., Nelson, M. and B. Rasnow. 1988 New technical approaches to m toring and interpreting the dynamics of real neural networks. IEEE Eng. Med. Biol. So Proceedings. 20: 1921-1922.

Wilson, M. and J. Bower. 1988 A computer simulation of olfactory cortex with functional im ations for storage and retrieval of olfactory information. Neural information p essing systems. D. Anderson, editor. AIP Press, New York, N.Y. pp. 114-126.

Invited presentations:

1990

Helmholtz Club, March, 1990, "O· ·tions in olfactory cortex in particular and cerebral cortex in general: Possible struc· l underpinnings and functional consequences".

Olfaction as a model system for c· ·tational neuroscience, Wellesley College, May, 1990, "Interdependent oscillations in · ·tory processing: A combined olfactory bulb olfactory cortex model".

Summer school on neural network· ·ay, 1990, Dubrovnik Yugoslavia, 3 lectures on the dynamics of the nervous system.

ETH, Zurich, Switzerland, May, 1· 2 lectures, "Associative memory and the olfactory system", "The structure of cere· ·r Purkinje cells".

The Brain, Cold Spring Harbor Sy· ·sium, June, 1990, "Modeling the olfactory system: Odor recognition, associative n· ·ry, and the pharmacological regulation of intrinsic connections within piriform (ol· ·ry) cortex".

Stanford University, June, 1990, "· illations in cortical circuits".

Albert Einstein College of Medici· June, 1990, Graduate Student Invited Seminar, "Computer Simulations and Ne· biology".

Gordon Conference on Mathemati· Biology, June, 1990, "Associative memory and cerebral cortical networks".

Aspen Center for Physics, Worksh· on Neural Networks, July, 1990.

Case Western University, "Functi· l organization of the Purkinje cell. Oct. 1990.

Marine Biological Laboratory, "A· ·ciative function in the mammalian olfactory system. Nov., 1990.

National Institutes of Health, "Mul· single neuron recording using silicon technology. Nov. 1990.

Second Annual Symposium on the F· ontiers of Science, National Academy of Science, Nov., 1990.

1989

The Rockefeller University: I. In· duction to the olfactory system: its anatomy, physiology, and computational p· blem; II. Computer simulations and multi-neuron recording: a computational appr· ·h to understanding the mammalian olfactory system. February 1989

Cornell University: I. Modeling a· ·aches to understanding neural systems. ; II. Reverse engineering the olfactory syste· Computer modeling approach. February 1989

Emergent Comput. ›n: Center for Nonlinear Studies, Los Alamos National Laboratories: Brain and paral computer maps. May 1989

Santa Fe Institute (nplex Systems Summer School: 5 lectures on dynamics in neural systems includi the olfactory system. June 1989

Neurocomputers a Attention: USSR National Academy of Science: Oscillations in cerebral cortica rcuits: Possible underlying mechanisms and functional consequences. September 198

Other Honors:

1990

Granted tenure, D. sion of Biology, California Institute of Technology

Appointed to the c orial board of Cognitive Brain Research.

1989

Appointed to the c orial board of the International Journal of Neural Systems.

Patents

none

Software Products

none

Graduate Students and Post Doctoral Fellows through contract period

Graduate Students - male (11)

Tom Annau (Majority)*
Chris Assad (Majority)
J.J. Banik (Indian) *
Upinder Bhalla (Indian) *
David Kewley (Majority)*
Maurice Lee (Asian-Amer[illegible])
Alex Protopapas (Majority)
Brian Rasnow (Majority)
John Thompson (Majority)
Mike Vanier (Majority) *
Matt Wilson (Asian-Amer[illegible]) *

Graduate Students - female (2)

Mitra Hartman (Majority)
Josee Morissette (French C[illegible]adian)

Post Docs - male (5)

Erik DeSchutter (Majority)
Mike Hasselmo (Majority)
Dieter Jaeger (German)
Mark Nelson (Majority) *
Mike Paulin (New Zealand[illegible])
Michael Speight (English)*

Post Docs - female (3)

Giri Gundappa-Sulur (Indi[illegible])
Leila Posakony (Hispanic)
Caroly Schumway (Majority)

* involved in ONR related projects

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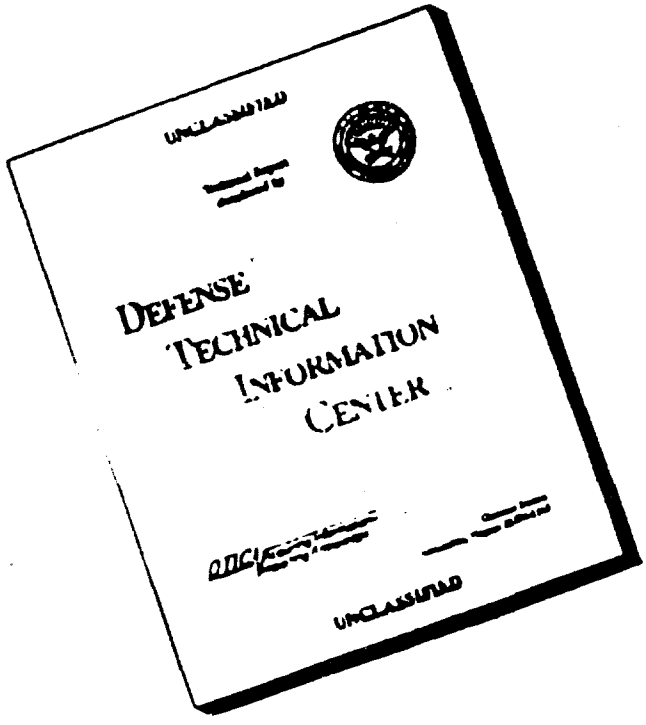

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